THE STOCHASTIC METHOD AND THE STRUCTURE OF PROTEINS

By Linus Pauling

Mr. President, Ladies and Gentlemen:

It is a great honor for me to have been invited to speak at
the opening session of the Thirteenth International Congress of Pure and
Applied Chemistry, and I express my thanks to the officers of the Con-
gress and of the International Union of Pure and Applied Chemistry for
having extended the invitation to me and to you and for your courteous
welcome.

My subject today is the stochastic method and the structure
of proteins. Many scientists have been interested in the question of
the way in which scientific discoveries are made. A popular idea is that
scientists apply their powerful intellects in the straightforward, logi-
cal induction of new general principles from known facts, and deduction
of previously unrecognized conclusions from known principles. This
method is, of course, sometimes used; but as a rule the advances in
knowledge that are made by it are less significant than those that

result from mental processes of another sort - in large part sub~~conscious~~ [conscious]

processes. Henri Poincaré, in his essay on mathematical creation, ~~written~~

~~years ago~~ said that knowledge of mathematics and of the rules of

logic is not enough to make a man a creative mathematician/ ~~Axgxifixofx~~ [- he must also

~~intuition~~
be gifted with an intuition that permits him to select from among the

infinite number of combinations ~~with~~ of mathematical entities already known,

most of them absolutely without interest, those combinations which will

lead to useful and interesting results. He illustrated the role of the

subconscious by describing his investigations of ~~~~ the Fuchsian

functions, which he had discovered while working at Caen. He left Caen

on a geologic excursion, and for some time, while traveling, made no

conscious effort to attack the problem; then one day, as he put his foot

on the step of an omnibus, the idea suddenly came to him th t the trans-

formations that he had used to define the Fuchsian functions were identical

with those of non-Euclidian geometry. He ~verified this ~~conclusion after on~~ [later]

~~his return to Caen. Then, after a period of non-productive effort, he~~

~~spent a few days at the seaside, and one morning, while walking on the~~

b̶h̶u̶f̶f̶y̶x

The field of the determination of the structure of crystals

by the x-ray diffraction t̶e̶c̶h̶n̶i̶q̶u̶e̶ method i̶s̶ provides interesting il-

lustrations of the ways that scientific progress is achieved. Work in

this field consists in the solution of individual, largely unrelated

problems - the determination of the a̶t̶o̶m̶i̶c̶ atomic arrangement of individual

crystals. If the atomic arrangement (the structure) is sufficiently simple

from the observed x-ray diffraction pattern

it can be determined/by straightforward, completely logical arguments.

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The procedure developed by Nishikawa, Wyckoff, and Dickinson before 1920

consisted in the tabulation, with use of the theory of space groups, of

all atomic arrangements compatible with the symmetry and size of unit

required to account for the x-ray pattern, and the rigorous elimination

with use of the observed x-ray intensities (especially of qualitative

inequalities in intensity of pairs of diffraction maxima) of all of these

atomic arrangements except one, which was then accepted as the structure

of the crystal. During the dozen years after the determination of the

first crystal structures by W. L. Bragg and W. H. Bragg most structure

determinations were made in this way.

It is well known that the electron distribution in a crystal can
be expressed as a three-dimensional Fourier series in which the coefficients
of the various Fourier terms are proportional to the square roots of the
intensities of ~~the~~ corresponding diffraction maxima. The ~~series~~ electron-
distribution function ^also^ depends, however, on the phases of the Fourier
terms, and there is no/~~general~~ ^generally applicable experimental^ method of determining these phases. For
a crystal of even moderate complexity, such as an amino acid, the number
of possible atomic arrangements provided by the theory of space groups is
so great that the exhaustive consideration of them and elimination of all
but one/ by use of the observed x-ray intensities/ cannot be carried out
even with the aid of electronic calculating machines, and the attack on
the ~~problemsofxthe~~ problems presented by these crystals must be made in
other ways.

During the first few years of my activity as a research man I
carried through a number of structure determinations by the rigorous method,
^in part^ in collaboration with my teacher Roscoe G. ~~Dickinson~~ Dickinson/ and ^in part^
independently. I was deeply interested, however, in more complex substances

than those that could be ~~attacked~~ (successfully investigated) in this way, and from 1928 on I

~~was successful in~~ ~~applying~~ (applied) a different method of attack to many substances.

One evening in 1933, after I had described the new method of crystal struc-

ture determination to him ~~in his home in New York~~, and contrasted it with

the rigorous method, Dr. Karl ~~Kandxkelmx~~ (K.) Darrow suggested that I

call it the stochastic method, and referred me to the introduction of this

expression by the chemist Alexander Smith, who had written, in his "Inor-

ganic Chemistry", 1909, page 142, the following: " .... When Mitcherlich

discovered that Glauber's salt gave a definite pressure of water vapor,

he at once formed the hypothesis, that is, supposition, that other

hydrates would be found to do likewise. Experiments showed this supposition

to be correct. The hypothesis was at once displaced by the fact. This

sort of hypothesis ~~prem~~ ~~predicted~~ predicts the probable existence of

certain facts or connections of facts, hence reviving a disused word,

we call it a stochastic hypothesis (Greek ~~stochastices~~ στοχαστικός, apt to devine the

truth by conjecture). It differs from the other kind in that it professes

to be composed entirely of verifiable facts and is subjected to verification

as quickly as possible." In the stochastic method of treating very complex

crystals a plausible structure is ~~guessed~~ (guessed) with the aid of hints provided

The stochastic method is, of course, used all the time by the organic chemist. He synthesizes a new substance and assigns it a structure — a stochastic structure — on the basis of his knowledge of chemical principles. Then he checks a few points — ultimate analysis, molecular weight, presence of a methoxy group or carboxyl group — and is satisfied that his guess is correct if the results of the tests are those that he has predicted.

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by the observed size of unit and space-group symmetry, ~~and~~ *as well as* knowledge of

general principles of molecular structure, and the stochastic hypothesis

that this is the actual structure of the crystal thereupon is either veri-

fied or disproved by the comparison of calculated and observed x-ray

intensities.

As a rule, if
/The agreement between observed *and* calculated intensities is excellent

the proposed structure may be accepted as the correct one. There is, however,

always some possibility that the agreement is fortuitous. This was em-

phasized by a discovery that Dr. M. D. ~~Shape~~ Shappell and I made in 1930, [1]

during our study of the structure of bixbyite $(Mn, Fe)_2O_3$, and the C-

modification of the rare-earth ~~sesquioxides~~. W. H. Zachariasen had in-

vestigated these crystals, and had assigned positions to the 32 metal atoms

in the unit cube. [2]   During our reinvestigation of the structure we

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[2] W. H. Zachariasen, Z. Krist., 67, 455 (1928)

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[1]
L. Pauling and M. D. Shappell, Z. Krist., 75, 128 (1930).

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discovered that the space group T_h^7 provides certain pairs of physically

distinct arrangements which give exactly the same intensities of reflection

of x-rays from all crystallographic planes, so that no unambiguous struc-

ture determination can be made by the consideration of x-ray intensities

alone. This ambiguity, which has not turned out to be an important one in

practice, has been further investigated by A. L. Patterson.

I shall content myself with a few examples of the application

of the stochastic method.

The mineral enargite, Cu_3AsS_4, was found on x-ray investigation[3]

to have an orthorhombic unit of structure with a = 6.46 Å, b = 7.43 Å,

and c = 6.18 Å. This unit contains six copper atoms, two arsenic atoms, and

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L. Pauling and S. Weinbaum, Z. Krist., 88, 48 (1934).

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eight sulfur atoms. The dimensions are closely similar to those of the

hexagonal mineral wurtzite, ZnS: the dimensions of a double orthohexagonal

unit of wurtzite, containing eight zinc atoms and eight sulfur atoms,

are $\sqrt{3}/\frac{a}{=}$ 6.65 Å, 2a = 7.68 Å, and c = 6.28 Å. This suggests that the

atomic arrangement ~~of enargite~~ is that shown in Figure 1, which results from replacing

one fourth of the zinc atoms in wurtzite by arsenic *atoms* and the remaining

three fourths by copper atoms, in such a way as to give discreet AsS$_4$

groups. It was found that the calculated/intensities x-ray for ~~this ideal~~ *postulated*

structure well
~~arrangement~~ agree ~~closely~~ with the observed ~~ones~~, and somewhat improved

agreement is obtained by moving the sulfur atoms slightly closer to the

arsenic atom and away from the copper atoms, giving the distances 2.2Å for arsenic-

sulfur and 2.32 Å for copper-sulfur. Although the structure depends

upon thirteen parameters, there is little doubt that it is correct.

A similar investigation, with, however, different results, was

carried out for the mineral sulvanite.[4] Sulvanite, Cu$_3$VS$_4$, has been

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[4]L. Pauling and R. Hultgren, _Z. Krist._, 84, 204 (1933).

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found as a massive mineral in Burra Burra, Australia, and in cleavable

masses and a few small crystals near Mercur, Utah. It ~~was found~~ to be

cubic, with unit of structure with a = 5.370 Å, containing three copper

atoms, one vanadian atom, and four sulfur atoms. The fact that the unit

of structure of the cubic form of zinc sulfi̱e has a = 5.42 Å and contains

four zinc atoms and four sulfur atoms strongly suggests that sulvanite has a

similar structure, with copper atoms replacing three of the zinc atoms

and vanadium the fourth. It was immediately noted, however, that the

observed intensities differ greatly from those calculated for this struc-

ture; the stochastic method in this case has failed. There is, moreover,

no other plausible structure that suggests itself. Fortunately,

the crystal is simple enough to permit the rigorous method of structure

determination to be applied. Its application was found to lead to the

structure shown in Figure 2.

This structure is a surprising one - it puzzles me nearly as

much today as it did twenty years ago, when it was discovered. The

four sulfur atoms are in the same positions as for sphalerite, and the

three copper atoms are in the positions occupied by three of the four zinc

atoms in sphalerite. The position of the fourth zinc atom remains,

however, unoccupied; instead, the vanadium atom is squeezed

~~introxthexsonixxxxity~~

in *a* position on the same side of the sulfur atoms as that toward which

the sulfur-copper bonds extend, rather than the opposite side, which would

complete the tetrahedral configuration of metal atoms about the sulfur atom.

This structure is satisfactory in that each metal atom is sur-

rounded tetrahedrally by sulfur atoms. It is surprising, however, that

the bonds formed by the sulfur atoms are not ~~wirx~~ tetrahedrally directed.

The explanation of the stability of this peculiar atomic arrangement may

lie in the formation of/weak covalent bonds between the vanadium atom and

the six surrounding copper atoms, and also in the Coulomb stabilization

of this structure, relative to the structure similar to that of sphalerite,

through the achievement of a small negative electric charge by the copper

atoms and a small positive charge by the vanadium atoms, which would result

from the formation ~~by the vanadium atoms of single~~ of metal-sulfur bonds with ~~the four~~ a considerable

~~sulfur atoms, and by the copper atoms of bonds with approximately 50 per~~

~~cent~~ amount of covalent character, with ~~the four sulfur atoms.~~

One of the most complex crystal structures to have been discovered

is that of zunyite.[5] Zunyite is an aluminosilicate that occurs as

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[5]L. Pauling, Z. Krist., 84, 442 (1933).

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colorless, transparent tetrahedra, about as hard as quartz. The mineral

has been found in San Juan County, Colorado, intimately mixed with guiter-

m̲i̲n̲ate, a lead arsenate, and in Ouray County, Colorado, in an altered

porphyrite; sharp crystals of zunyite have also been found with hematite

as powder in pots from graves in Uaxactun, Guatemala. Its composition

could not be determined from the chemical analyses until the x-ray studies

had been made, which ~~inixxox~~ provided a determination of the formula

weight. The cubic unit of structure was found to have $\underline{a}$ = 13.82 Å,

and to contain four molecules of composition $Al_{13}Si_5O_{20}(OH, F)_{18}Cl$.

It was known in 1933 that in all silicates investigated up to that time

each silicon atom ~~was~~ is surrounded tetra~~hedrally~~ by four oxygen atoms, with

the silicon-oxygen distance about 1.60 Å, and that aluminum atoms ~~were~~ are

usually surrounded octahedrally by six oxygen atoms, with aluminum-oxygen

distance 1.90 Å, although a tetrahedral environment of aluminum atoms had

also been observed in a few minerals.

~~was also occasionally found.~~ It was not easy to find a way of combining

tetrahedra and octahedra by the sharing of corners and edges to give a

for zunyite,

cubic structure with the right dimensions, but finally a single structure

(Figure 3),

x-ray

was discovered∧ and the calculated/intensities for the structure were

structure

found to be in good agreement with experiment. In this ~~xkruxxkrx~~ structure there

in the crystal

are complexes of twelve aluminum octahedra, which are held together/by

sharing corners with one another, and also with a single aluminum tetra-

hedron and a complex of five silicon tetrahedra. This tetrahedron-octa-

hedron framework defines cavities which are occupied by chloride ions.

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The structures of many other minerals (topaz, mica, ɟkaolinite,

∧

chlorite, swedenborgite, etc.) were∧determined by the stochastic method.

During recent years a number of complex intermetallic compounds

have been successfully investigated ~~by~~ in the same way. A fundamental

structural principle for metals and alloys is that in general each atom

surrounds itself by as many neighbors as possible. Some of the most in-

teresting metal structures that are known have been discovered as a

result of the recognition of the significance of polyhedra of the icosa-

hedral group. These polyhedra, which have five-fold axes of symmetry

as well as three-fold axes and two-fold axes, cannot, of course, retain

their symmetry elements completely in crystals, which cannot have true

the icosahedral polyhedra

five-fold axes. However, it is found that ~~they~~ can be present in crystals

with only slight deformation.

It is interesting that the icosahedral arrangement of twelve

atoms around a central atom provides what may be called a closer packing

than closest packing - that is, than closest packing of spheres of the

same size. In the icosahedral configuration the central atom can be

10 percent smaller than the twelve surrounding atoms, which are still

able to make contact with it.~~byxassumingxpasitions~~ The most complex

~~intermetallicxcompounds~~ metal structure ~~to have been determined~~ is that

of $Mg_{32}(Zn, Al)_{49}$. In this crystal a central atom is surrounded by

6   G. Bergman, J. L. T. Waugh, and L. Pauling, Nature 169, 1057 (1952).

an icosahedron of twelve slightly larger atoms. This group of thirteen

(Fig. 4).

atoms is then surrounded by twenty atoms, at the corners of a pentagonal

dodecahedron ~~★★★★~~, x each of these twenty atoms thus lying directly out

from the center of xx one of the twenty faces of the icosahedron. The

next twelve atoms lie out from the centers of the pentagonal faces of

the dodecahedron; this gives a complex of forty-five atoms, the outer

thirty-two of xx which lie at the corners of a rhombic triacontahedron.

The next shell ~~afxatomxxconxx~~ consists of sixty atoms, each directly out

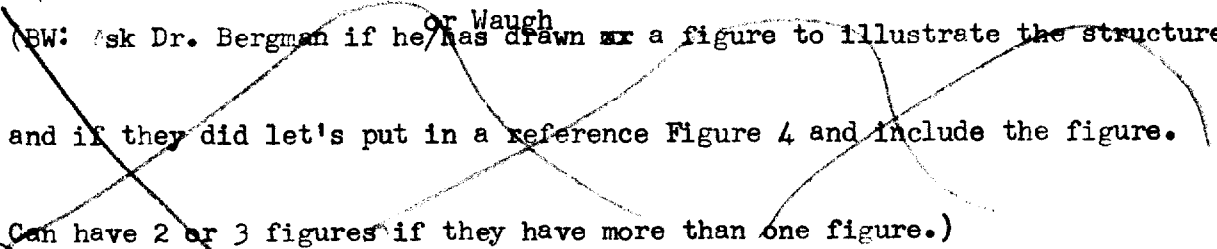from the the center of a triangle which forms one half of one of the

thirty rhombs bounding the rhombic triacontahedron; Their these sixty

atoms lie at the corners of a truncated icosahedron, which has twenty

hexagonal faces and twelve pentagonal faces. Twelve additional atoms

are then located out from the centers of twelve of the twenty hexagonal

faces. The very large complexes are then condensed together, with their centers at

the point of a body-centered cubic lattice, in such a way that each of

the seventy-two outer atoms is shared between two complexes; each then

contributes thirty-six atoms per lattice point, which with the central

complex of forty-five atoms gives eighty-one atoms per lattice point,

or 162 in the unit cube.

The complexity of this structure may be attributed to the dif-

ficulty of fitting complexes with icosahedral symmetry into a crystal

with cubic symmetry.

It seems not unlikely that the complexity of the simplex

intermetallic compound with the simple formula $NaCd_2$ is to be attributed

to the same cause. I have now been working on the problem of the struc-

ture of this crystal for thirty years, and the structure still remains

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L. Pauling, J. Am. Chem. Soc., 45, 2777 (1923).
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undiscovered. The crystal is cubic, with the edge of the unit cube slightly

over 30 Å. This unit contains about 384 sodium atoms and 768 cadmium

atoms. The attempt to determine its structure by rigorous methods would,

of course, be hopeless; but I think that the stochastic method will ulti-

mately be successful.

(BW: Ask Dr. Bergman if he/has drawn a figure to illustrate the structure

and if they did let's put in a reference Figure 4 and include the figure.

Can have 2 or 3 figures if they have more than one figure.)

The power of the stochastic method is illustrated by its recent

application to the p roblem of the configuration of polypeptide chains in

proteins. The history of this application is illuminating also in showing

that an investigator who strives to apply the method must have confidence

in himself. In 1937, after I had become interested in proteins, and had

carried out a number of experimental studies of their properties (especially

the magnetic properties of hemoglobin) and, with Dr. Alfred Mirsky, had

formulated a general theory of the structure and process of denaturation

of proteins[8], I spent several months in an unsuccessful effort to apply the

stochastic method in the discovery of an acceptable structure for α keratin.

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[9] A. E. Mirsky and L. Pauling, Proc. Nat. Acad. Sci., 22, 439 (1936).
[7] L. Pauling and C. D. Coryell, Proc. Nat. Acad. Sci., 22, 210 (1936).

It was possible at that time to predict that the amide group in a peptide

would be planar, because of the resonance of the double bond between the

two positions C-O and C-N, and it was possible to predict the interatomic

distances and bond angles, essentially as given in Figure 5, with reasonable

confidence. In addition it was recognized that a stable configuration

would be the formation of hydrogen bonds between the

N-H group and the oxygen atom of the carbonyl group, with N-H•••O distance

approximately 2.80 Å. No reasonable configuration was found in this early

investigation, however, and in consequence the possibility was considered

that the structural parameters of the polypeptide chain might be sig-

nificantly different from those predicted from information obtained through

the determination of the structures of somewhat dissimilar sub-

stances. At that time no structure determination had been made of any

amino acid, simple peptide, or other simple substance closely related to

proteins. My colleague Professor Robert B. Corey, who had some

years earlier made x-ray photographs of several proteins (with R. W. G.

Wyckoff) and I concluded that we should em-

bark upon a program of precise structure determination of these simple

substances. This program has been/under way since 1937, and has led
steadily

to the/determination of the structures of crystals of half a dozen amino
precise

acids, several simple peptides, and several other simple substances (such

as acetylglycine) closely related to proteins. ~~inxanxxxnitxnfxthixxxark~~

Through these investigations it was found that the planarity of the amide

group and the interatomic distances and bond angles are *in fact* preserved in all

of the simple substances and can confidently be expected to apply also

to the polypeptide chains in proteins. In addition, hydrogen bonds with

N–H∙∙∙O distance 2.79 ± 0.12 Å have been found to be ~~pxx~~ universally

present.

Even after this program was well under way, and ~~the dimensions~~

~~of the structural features predicted for the polypeptide chain~~

it was recognized that the structural parameters of the polypeptide chain

could be reasonably well predicted, there was delay in the application

of the stochastic method to the problem of the structure of proteins.

This delay probably resulted from the failure of the earlier effort and

from the feeling that the chemical complexity of the proteins – their

construction from about twenty different kinds of amino–acid residues –

might well indicate a corresponding structural complexity. Then one day

in March 1948, while I was ~~laid in bed~~ at my home in Oxford (where I was

serving as Eastman Professor) ~~to~~ recuperate from a cold, I decided/to again

attack the problem of the configuration of polypeptide chains, for the

first time in eleven years. It occurred to me to make a search for the

simplest configurations - those in which all of the amino-acid residues

are structurally equivalent. The most general operation that converts an

into an equivalent element

asymmetric element (~~such as~~ not its ~~enantiomer~~ mirror image) is a

rotation about an axis combined with a translation along the axis. The

repetition of this general operation automatically leads to a helix.

helical
I attempted accordingly to find/configurations of polypeptide chains in-

volving planar amide groups with known dimensions, such that suitable ~~helical~~

of
hydrogen bonds were formed. Within an hour, with the aid ∧ a pencil and

a piece of paper, I had discovered a satisfactory helical structure. It

did not, however, explain ~~satisfactorily~~ the details of the x-ray diagram

of hair and other α-keratin proteins, and nothing more was done along

these lines for some months.

After my return to Pasadena, Professor Corey and I suggested

to Dr. H. R. Branson, a young man interested in the application of

mathematics to ~~p~~ chemical problems, that he make a search for other satisfactory

helical configurations. He found/one, ~~xtharxxstraxhxxx additional satisfactory~~
only

~~configuration,~~ and in 1951 a description of the two helixes, the α helix

and the γ helix, was published.[10]

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[10] L. Pauling, R. B. Corey, and H. R. Branson, ~~xxAmxxChemxxSamxxx~~ Proc.
Nat. Acad. Sci., 37, 205 (1951).

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(Figure 6),

Although the α helix, which has about 3.6 amino-acid residues

per turn and a pitch of about 5.4 $\overset{o}{A}$, did not explain in an obvious way

the ~~xhx~~ principal feature of the x-ray diagram of the α-keratin proteins,

a strong meridional reflection with spacing 5.15 $\overset{o}{A}$, its predicted x-ray

pattern was found to be in excellent agreement with the observed pattern

for synthetic polypeptides. Moreover, the general similarity in appear-

ance of the x-ray diagram for the α-keratin proteins and that for the

synthetic polypeptides gave reasonably strong support to the assignment

of the α helix to these fibrous proteins also. The problem of the

origin of the 5.15 Å meridional reflection seems to have been solved

by the simultaneous suggestion by F. H. C. Crick,[10] and Professor

Corey and me[8] that in the α-keratin proteins the α helixes are twisted

about one another. A detailed structure is that shown in Figures 7 and 8;

it involves the seven-strand cable of α helixes, with two additional

α helixes in the interstitial positions.

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[10] F. H. C. Crick, Nature, 170, 1882 (1952)

[11] L. Pauling and R. B. Corey, Nature, 171, 59 (1953).

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Reasonably convincing evidence has also been obtained, largely

through the work of Perutz and Kendrew, who have studied hemoglobin and

myoglobin, and of Riley and Arndt, who have prepared radial-distribution

curves of a number of proteins, that/globular proteins contain many

with the configuration of the α helix. In hemoglobin and myoglobin these

α-helix segments lie in approximately parallel orientation to one another.

No detailed information ~~ixxasxyxix~~ has so far been obtained about the

way in which the polypeptide chains make the transition from one α-helix

segment to another.

Silk fibroin is shown by its x-ray diagram to have a structure

which repeats in the distance 7.00 Å along the fiber axis. The antiparallel

chain pleated-sheet structure, shown in Figure ~~4-9~~ 9, is predicted to have

the identity distance 7.00 Å along the fiber axis, and in other respects

it accounts satisfactorily for the x-ray diagram of silk fibroin; it can

be confidently accepted as representing this protein. It is probable

that the β-keratin proteins (such as stretched hair) have a closely similar

structure, with, however, the ~~staggered~~ polypeptide chains ~~alternatingxin~~

~~orientationxxwithxxhx~~ ~~___~~ in parallel, rather than antiparallel, orientation.

The x-ray diagram of collagen and gelatin is characteristic of

these proteins, showing that they have a structure different from that of

α-
the proteins of the/keratin class, and also different from that of silk

and the β-keratin proteins. The stochastic method was used in the formula-

tion of a structure for collagen and gelatin~~12~~ 13, which, however, has since

been found to be in disagreement with some of the features of the x-ray

diagram.   Despite much effort that has been expended on the problem,

13 12 L. Pauling and R. B. Corey, Proc. Nat. Acad. Sci., 37, 272 (1951)

no satisfactory structure for collagen and gelatin has ~~//~~ yet been found.

The problem of the structure of collagen and gelatin may be used to illustrate an important aspect of the stochastic method. The first step in the application of this method is to make a ~~guess~~ hypothesis - a guess. The second step is to test the hypothesis, by some comparison with experiment. In general the test cannot be sufficiently thorough to provide ~~absolute~~ rigorous proof that the ~~hypothesis~~ hypothesis is correct - it may easily be shown that the hypothesis is incorrect, ~~but~~ through the discovery of a significant disagreement with experiment, ~~but~~ agreement on a limited number of points cannot be accepted as verification of the hypothesis. In order for the stochastic method to be significant/ the principles used in formulating the hypothesis must be restrictive enough to make the hypothesis itself essentially unique; in other words, ~~every~~ an investigator who makes use of this method should be allowed one guess. If he were allowed many guesses he would sooner or later make one that was not in disagreement with the limited number of test points, but there would then be little justification for accepting that ~~hypothesis~~ guess as correct. I may, however, contend that Professor Corey and I should ~~be~~ be allowed two guesses on together

~~now be allowed a secon~~ ~~guess on~~ collagen, ~~because together we could do~~

~~me~~ and we are determined that our second one shall be right.

We may ask whether or not the quality of simplicity in postulated explanations of natural structures and phenomena is to be required. It is clear that living organisms are not simple, and yet there is a striving for simplicity — the use of the same structural element or mechanism over and over again; the ~~use~~ hem groups in hemoglobin, cytochrome, and other conjugated proteins; L ~~amino~~ acid residues instead of a mixture of L and D; the use of structural complementariness in antigen-antibody interaction, gene reduplication, enzyme activity, and other phenomena.

Perhaps the time has come to ~~foster a~~ carry out a penetrating study of the principles of the stochastic method, in order to get a better understanding of it, to make it more powerful. The problems of biology and medicine are of great importance to man, and they are so difficult that we cannot afford to overlook any possible aid in their solution.
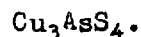
Legends for Figures

Fig. 1. The structure of enargite,/ Cu_3AsS_4. The large circles re-present sulfur atoms, the small circles copper atoms, and the small

shaded circles arsenic atoms.

Fig. 2. The structure of sulvanite, Cu_3VS_4.

Fig. 3. A portion of the structure of zunyite, $Al_{13}Si_5O_{20}(OH, F)_{18}Cl$.

AlO_6 groups are represented by octahedra, and SiO_4 and AlO_4 groups by

tetrahedra, the last being marked Al. Smaller spheres represent oxygen

atoms, larger spheres chloride ions. Groups of five tetrahedra and

twelve octahedra preserve their identity in the structure.

Fig. 4 on recond

Fig. 5. Diagrammatic representation of the configuration

of the polypeptide chain in the α helix.

Fig. 6. The α helix.

Fig. 7. At the left, a compound α helix - an α helix whose

axis describes a helical configuration. The diameter, shown as about 10 Å,

includes the volume occupied by side chains as well as the main chains

of the protein. Center, a 7-strand α-cable. In the proposed structures

of proteins of the α-keratin type these rather cables are packed together,

with compound helixes as shown at the left in the interstices. At the

right, a 3-strand rope of α helixes.

Fig. 5. A cross section of the α-keratin structure, showing

the 7-strand α-cables AB_6 and the interstitial compound helixes C.

The orientation of the cross-section of the cable changes with coordinate

along the fiber axis. The central cable is shown in the most unfavorable

orientation for the interstitial α helixes. The protein chains are not

so nearly circular in cross section as indicated in the drawing, and

space is filled more effectively than is indicated.

Fig. 9. Drawing representing the antiparallel-chain pleated-sheet

structure.

Fig. 4. The structure of the intermetallic compound $Mg_{32}(Zn,Al)_{49}$. The six drawings, from left to right in the top row and then left to right in the bottom row, have the following significance: a central atom surrounded by a nearly regular icosahedron; twelve atoms at the points of the icosahedral group of thirteen atoms surrounded by a pentagonal dodecahedron; twenty atoms at the points of the complex of thirty-three atoms surrounded by twelve atoms at the corners of an icosahedron; the outermost shell of sixty atoms at the corners of a truncated icosahedron, plus twelve atoms out from the centers of twelve of the hexagons of this polyhedron; packing drawing showing the complex of forty-five atoms plus an outer shell of seventy-two atoms; the structure of the crystal, in which these complexes located about the points of a body-centered cubic lattice share all of the seventy-two atoms of the outermost shell with neighboring complexes.